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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 02D-0258
Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations

Dear Sir/Madam,

As a company actively engaged in the drug development process, Pharmacia appreciates FDA's issuance of the draft guidance for industry, "*Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*" (July 11, 2002, FEDERAL REGISTER, page 45983). Our comments on this guidance are outlined below.

To facilitate review of future revisions of existing guidances, the agency should consider making a "track changes" version of the guidance available for review by sponsors.

Page 7 Section III.A.1 General Considerations
There should be a distinction made between a "crossover" study design (same subjects receiving test and reference treatments) and a "balanced randomized crossover" which has further implications on data analysis.

Page 9, Section III.A.8.c. Total Exposure
Clarification is needed for definition of t in AUC0-t. As presently worded ("*...t is the last time point with measurable concentration for individual formulation*"), t could be interpreted as the last time point at which ALL subjects had a measurable concentration for a given formulation, rather than the last time point with a measurable concentration for an individual subject / treatment profile. 02D-0258 C2

Page 10, Section III D In Vitro Studies
We do not agree that BE determinations for pharmaceutical equivalence assessments in ANDAs should be made based on dissolution data alone, even for high permeability, high

solubility drugs. Since ANDAs for solid oral dosage forms represent new formulations and/or materials from new suppliers, the minimum standard for BE should be a human pharmacokinetic trial.

Page 11, Section III D In Vitro Studies
The recommendations for dissolution media should be consistent with those in the FDA *Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.* That document recommends the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. The agency should also consider stating the use of 0.01N HCl rather than 0.1 N HCl to provide a pH environment more representative of the fasted conditions in the stomach (pH 1.4 - 2.1)[1] and to reflect current trends in industry practice.

The sentence "Water can be used as an additional medium" should not be included. This statement contradicts the recommendation in the FDA *Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms* that "Use of water as a dissolution medium also is discouraged because test conditions such as pH and surface tension can vary depending on the source of the water and may change during the dissolution test itself, due to the influence of the active and inactive ingredients."

We suggest the following sentence be reworded: "The agitation speed and medium that provide the best discriminating ability, taking into account all the available in vitro and in vivo data, will be selected." The term "best discriminating ability" suggests that the dissolution method that is most sensitive to formulation variables, manufacturing variables, and in vivo performance be selected. This approach will typically lead to either an over-discriminating test or an unacceptably low specified Q-value. We recommend the sentence be reworded as follows: "The agitation speed and medium that provide appropriate discriminating ability, taking into account the available in vitro and in vivo data, be selected and justified."

Page 12, Section V Documentation of BA and BE
In the 2nd and 3rd bullet points, it is unclear whether the parenthetical comments regarding SUPAC are meant to limit the application of biowaivers to Level I changes only, or to allow biowaivers for changes up to, and including, Level II. This should be clarified.

Page 13, Section V.C.2.a INDs, NDAs and ANDAs: Preapproval
The last paragraph suggests that dissolution profiles in only one medium are usually appropriate to support biowaivers for a different strength of an immediate-release capsule or tablet that is proportionally similar to a suitable reference, when an appropriate dissolution method has been established. Otherwise, dissolution data in three media are recommended.

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[1] Dressman, J.B., Physiological aspects of the design of dissolution tests. In G.L. Amidon, J.R. Robinson, and R.L. Williams. Scientific Foundations for Regulating Drug Product Quality. AAPS Press, 1997, pp. 155-168.

We note that in order to develop an appropriate dissolution method, Section III.D of this Guidance recommends dissolution profiles on all strengths in at least three dissolution media be performed. Therefore, there is no practical advantage to only recommending dissolution data in one medium.

Page 14, Section V.C.2.a INDs, NDAs, and ANDAs: Preapproval
The second paragraph should be changed from "For an ANDA, conducting an in vivo study on a strength that is not the highest may be appropriate for reasons of safety....." to "For an ANDA, biowaiver of a higher strength will be determined to be appropriate provided that the following ....." This language would reflect parity with that for NDAs, since safety reasons should not be a special consideration for ANDAs only.

Page 14, Section V.C.2b NDAs and ANDAs: Postapproval
The sentence " For postapproval changes, the in vitro comparison should be made between the prechange and postchange products" should be amended to say "For postapproval changes, the in vitro comparison should be made between the prechange and postchange products for NDAs, and for ANDAs between the postchange and reference listed drug products...."

Page 15, Section V.D.1 NDAs: BA and BE Studies
We recommend the following change for clarity, from "§ 320.25 (f)(2),..., such as:" to "§ 320.25 (f)(2),..., appropriate reference materials could include:".

Page 17, Section V. E. Miscellaneous Dosage Forms
We do not agree with the last sentence, which states, "In general, in vitro dissolution test conditions for chewable tablets should be the same as for nonchewable tablets of the same active ingredient or moiety." Chewable tablets will typically have different inactive ingredients, include agents to either mask or add flavor, and be made by different manufacturing methods than the non-chewable product. In these instances, the in vitro test conditions for the non-chewable product provide a reasonable starting point for dissolution method development, but ultimately, the registered dissolution conditions should be developed and justified as described in Section III of this guidance. While this may result in the same dissolution methods being suitable for both the chewable and non-chewable tablets, it should not be assumed that this will be the case.

Page 18, Section VI.B.1. Parent Drug Versus Metabolites
The 3rd paragraph of this section does not specifically address BE studies of formulations in which the active ingredient is a prodrug. In this case, it should be stated that measurement of only the active moiety is recommended.

Page 19, Section VI.B.1 Parent Drug Versus Metabolites
In the second bullet point, second sentence "If the metabolite contributes meaningfully to safety and/or efficacy, the metabolite and parent drug should be measured" should be changed. The word "meaningfully" is subject to a broad set of interpretations, it is suggested instead that the wording be changed to "If the metabolite contributes to the toxicology or pharmacology profile, both the metabolite and parent drug should be measured."

Page 19, Section VI.B.2 Enantiomers Versus Racemates
The third sentence should be changed from "... when all of the following conditions are met:...." to "... when one or more of the following conditions are met:...."

Page 19, Section VI.B.3
In the last sentence, please clarify what is meant by "in vitro approaches." In vitro should not be restricted to dissolution testing.

Page 20, Section VI.C. Long Half-Life Drugs
The last sentence should be changed from "In such cases, sponsors and/or applicants should consult the appropriate review staff." to "In such cases, an AUC $_{0\text{-}t}$ or AUC 0-∞ should be used."

Page 22, Attachment A
Under "Study conduct", the recommended time for the fasting period before administration has not been specified. The 3rd bullet point should be reworded to "An adequate washout period...should separate consecutive treatment periods."

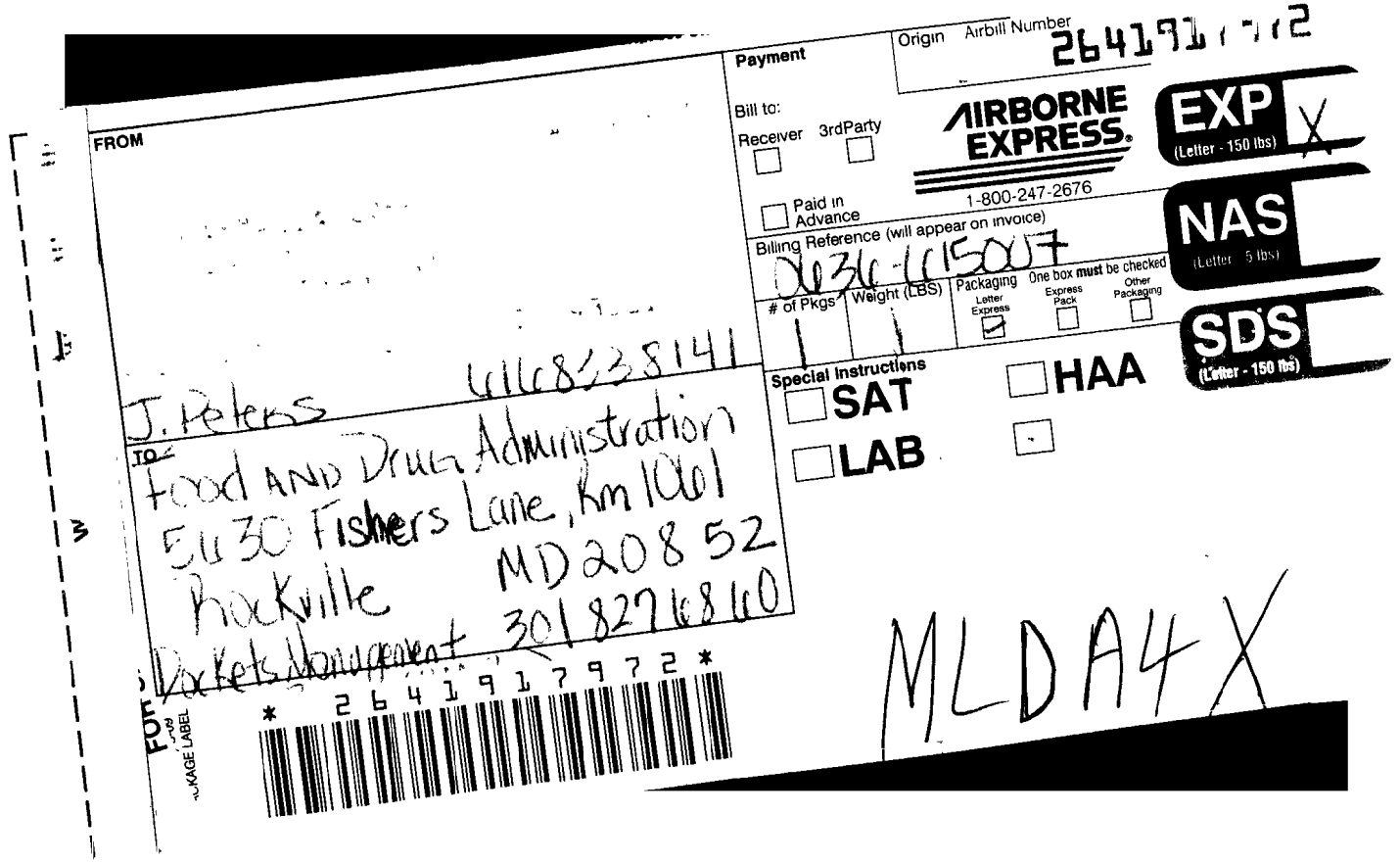
Page 23, Attachment A
It should be specified that the 1st bullet point refers only to a single-dose study. AUC0-τ for multiple-dose study should be added to 3rd bullet point under "The following pharmacokinetic information is recommended for submission:" and to the text above the last 2 bullet points on this page. In the 1st bullet point under "In addition, the following statistical information.....", it should be specified whether this refers to the ANOVA model-based geometric LS means.

Page 24, Attachment A
Clarification is needed that the first 2 bullet points are from the ANOVA model. More useful descriptions of these items would be "Ratio of geometric LS mean" and "90% Confidence interval for the ratio of geometric LS mean". In the last bullet point on this page, 90% should be inserted in front of CI.

We thank you for the opportunity to comment on this draft guidance. Please let us know if you have any questions on our review.

Sincerely,

Jenny Peters
Pharmacia Corporation



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Origin Airbill Number 264191[illegible]772

Bill to:
Receiver 3rdParty

AIRBORNE EXPRESS.

EXP (Letter - 150 lbs) X

Paid in Advance

1-800-247-2676

NAS (Letter - 5 lbs)

Billing Reference (will appear on invoice)

0036-615007

SDS (Letter - 150 lbs)

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1	1	✓		

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